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Chapter 31: Sickle Cell Disease

INTRODUCTION

- *Sickle cell syndromes* are hereditary conditions characterized by the presence of sickle hemoglobin (HbS) in red blood cells (RBCs).
- Sickle cell trait (SCT) is the heterozygous inheritance of one normal β-globin gene–producing hemoglobin A (HbA) and one sickle gene–producing HbS (HbAS). Individuals with SCT are usually asymptomatic.
- Sickle cell disease (SCD) can be of homozygous or compounded heterozygous inheritance. Homozygous HbS (HbSS) has historically been referred to as sickle cell anemia (SCA), which now also includes HbSβ^0-thal due to similarities in clinical severity. The heterozygous inheritance of HbS with another qualitative or quantitative β-globin mutation results in sickle cell hemoglobin C (HbSC), sickle cell β-thalassemia (HbSβ^+-thal and HbSβ^0-thal), and some other rare phenotypes.

CLINICAL PRESENTATION

- SCD is usually identified by routine neonatal screening programs using isoelectric focusing, high-performance liquid chromatography, or electrophoresis.
- Laboratory findings include low hemoglobin; increased reticulocyte, lactate dehydrogenase, platelet, and white blood cell counts; and sickled RBC forms on the peripheral smear.
- SCD involves multiple organ systems. Clinical manifestations depend on the genotype (**Table 31-1**).
- Cardinal features of SCD are hemolytic anemia and vasoocclusion. Symptoms are delayed until 4–6 months of age when HbS replaces fetal hemoglobin (HbF). Common findings include pain with fever, pneumonia, splenomegaly, and, in infants, pain and swelling of the hands and feet (eg, hand-and-foot syndrome or dactylitis).
- Clinical manifestations of SCD are due to impaired circulation, RBC destruction, and stasis of blood flow and ongoing inflammatory responses. Common clinical signs and symptoms of SCD include chronic anemia and pallor; fever; arthralgia; scleral icterus; abdominal pain; weakness; anorexia; fatigue; enlarged liver, spleen, and heart.
- Acute complications of SCD include fever and infection (eg, sepsis caused by encapsulated pathogens such as *Streptococcus pneumoniae*), stroke, acute chest syndrome, priapism, pain, splenic sequestration, and venous thromboembolism.
- Chronic complications involve many organs and include pulmonary hypertension, airway inflammation and hyperresponsiveness, bone and joint destruction, ocular problems, cholelithiasis, cardiovascular abnormalities, and renal manifestations.

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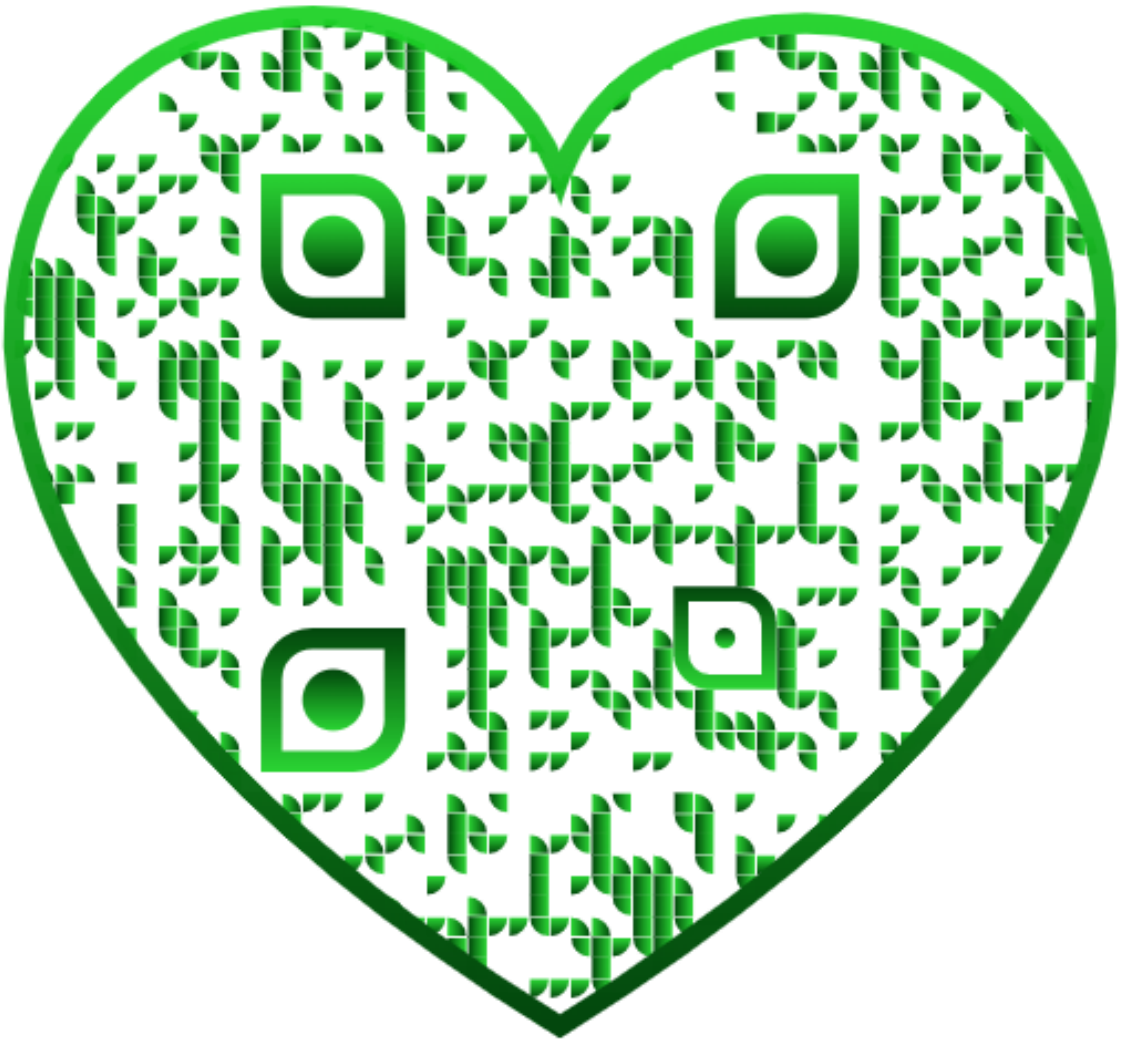

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TABLE 31-1

Clinical Features of Sickle Cell Trait and Common Types of Sickle Cell Disease

Type	Clinical Features
SCT	Rare painless hematuria; heavy exercise under extreme conditions can provoke gross hematuria and complications (normal Hb)
SCA-HbSS	Pain episodes, microvascular disruption of organs (spleen, liver, bone marrow, kidney, brain, and lung), gallstones, priapism, leg ulcers; anemia (Hb 6–9 g/dL [60–90 g/L; 3.72–5.59 mmol/L])
HbSC	Painless hematuria and rare aseptic necrosis of bone; pain episodes are less common and occur later in life; other complications are ocular disease and pregnancy-related problems; mild anemia (Hb 9–14 g/dL [90–140 g/L; 5.59–8.69 mmol/L])
HbSβ^{+}-thal	Rare pain; milder severity than HbSS because of the production of some HbA; Hb 9–12 g/dL (90–120 g/L; 5.59–7.45 mmol/L) with microcytosis
HbSβ^{0}-thal	No HbA production; severity similar to SCA; Hb 7–9 g/dL (70–90 g/L; 4.34–5.59 mmol/L) with microcytosis

TREATMENT

- Goals of Treatment: The goals are to reduce hospitalizations, complications, and mortality as well as to improve quality of life.

GENERAL PRINCIPLES

- Patients with SCD require lifelong interprofessional care that combines general symptomatic supportive care, preventative medical therapies, and specific disease-modifying therapies.
- Routine immunizations plus influenza, COVID-19, meningococcal, and pneumococcal vaccinations are recommended.

PHARMACOLOGIC THERAPY

- Prophylactic **penicillin** is recommended until at least 5 years of age. An effective regimen is penicillin V potassium, 125 mg orally twice daily until 3 years of age and then 250 mg orally twice daily until age 5 years.
- HbF reduces polymer formation of HbS. Increases in HbF correlate with decreased RBC sickling and adhesion. Patients with low HbF levels have more frequent pain and higher mortality. HbF levels of 20% or greater reduce the risk of acute sickle cell complications. **Hydroxyurea,** a chemotherapeutic agent, stimulates HbF production and increases the number of HbF-containing reticulocytes and intracellular HbF. It is indicated for patients 2 years of age and older with recurrent moderate to severe painful crises to reduce the frequency of pain crises and the need for blood transfusions. The recommended single daily dose for adults is 15 mg/kg and 20 mg/kg for children (**Fig. 31-1**).
- **L-Glutamine** is approved for patients with SCD age 5 and older to reduce the acute complications of SCD. Dose is weight-based: 5 g orally twice a day for <30 kg; 10 g orally twice a day for 30–65 kg and 15 g orally twice a day for >65 kg.
- **Crizanlizumab** is a monoclonal antibody against the adhesion molecule P-selectin. It is an IV solution approved for patients with SCD age 16 and older at a dose of 5 mg/kg IV every 2 weeks for 2 doses, followed by 5 mg/kg IV every 4 weeks.

FIGURE 31-1

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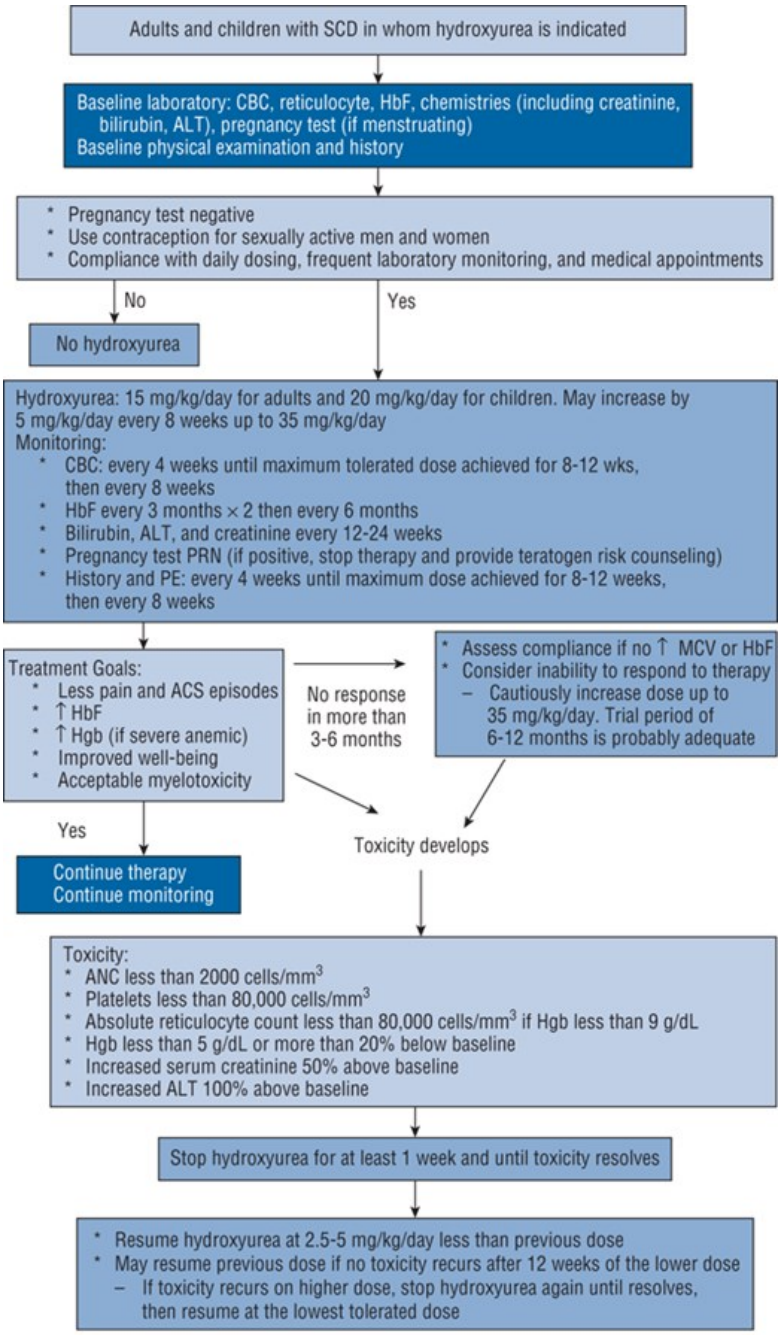
Hydroxyurea use in sickle cell disease. Blood test results expressed in SI units that are consistent with toxicity are <2 × 10^9/L for ANC; <80 × 10^9/L for platelets; <80 × 10^9/L for absolute reticulocyte count if Hb <90 g/L (5.59 mmol/L); and Hb <50 g/L (3.10 mmol/L). ALT, alanine aminotransferase; ANC, absolute neutrophil count; PE, physical examination; PRN, as needed.


Adults and children with SCD in whom hydroxyurea is indicated
Baseline laboratory: CBC, reticulocyte, HbF, chemistries (including creatinine, bilirubin, ALT), pregnancy test (if menstruating)
Baseline physical examination and history
* Pregnancy test negative
* Use contraception for sexually active men and women
* Compliance with daily dosing, frequent laboratory monitoring, and medical appointments
No
Yes
No hydroxyurea
Hydroxyurea: 15 mg/kg/day for adults and 20 mg/kg/day for children. May increase by 5 mg/kg/day every 8 weeks up to 35 mg/kg/day
Monitoring:
* CBC: every 4 weeks until maximum tolerated dose achieved for 8-12 wks, then every 8 weeks
* HbF every 3 months × 2 then every 6 months
* Bilirubin, ALT, and creatinine every 12-24 weeks
* Pregnancy test PRN (if positive, stop therapy and provide teratogen risk counseling)
* History and PE: every 4 weeks until maximum dose achieved for 8-12 weeks, then every 8 weeks
Treatment Goals:
* Less pain and ACS episodes
* ↑ HbF
* ↑ Hgb (if severe anemic)
* Improved well-being
* Acceptable myelotoxicity
No response in more than 3-6 months
* Assess compliance if no ↑ MCV or HbF
* Consider inability to respond to therapy
– Cautiously increase dose up to 35 mg/kg/day. Trial period of 6-12 months is probably adequate
Yes
Toxicity develops
Continue therapy
Continue monitoring
Toxicity:
* ANC less than 2000 cells/mm3
* Platelets less than 80,000 cells/mm3
* Absolute reticulocyte count less than 80,000 cells/mm3 if Hgb less than 9 g/dL
* Hgb less than 5 g/dL or more than 20% below baseline
* Increased serum creatinine 50% above baseline
* Increased ALT 100% above baseline
Stop hydroxyurea for at least 1 week and until toxicity resolves
* Resume hydroxyurea at 2.5-5 mg/kg/day less than previous dose
* May resume previous dose if no toxicity recurs after 12 weeks of the lower dose
– If toxicity recurs on higher dose, stop hydroxyurea again until resolves, then resume at the lowest tolerated dose

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Lisa M. Holle, Cecily V. DiPiro: *DiPiro's Pharmacotherapy Handbook, 13th Edition*
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OTHER THERAPIES

- Chronic RBC transfusions are indicated for primary and secondary stroke prevention and amelioration of organ damage. Transfusions are usually given every 3–4 weeks or as needed to maintain desired HbS levels. The optimal duration of primary prophylactic transfusion therapy in children is unknown. Risks include alloimmunization, hyperviscosity, transfusion-transmitted viral infections (requiring hepatitis A and B vaccination),

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volume and iron overload, and nonhemolytic transfusion reactions.

- Allogeneic hematopoietic stem cell transplantation is a curative therapy for SCD. The best candidates are younger than 16 years, have severe complications, and have human leukocyte antigen–matched donors. Risks must be carefully considered and include mortality, graft rejection, and secondary malignancies.

- **Exagamglogene autotemcel** and **lovotibeglogene autotemcel** are FDA approved gene therapies for SCD. Harvested stem cells are genetically modified ex vivo and then transplanted back to the patient after receiving myeloablative busulfan-based therapy. These modified cells repopulate the erythrocytes and alleviate disease complications through various mechanisms. Challenges include accessibility, high costs, toxicity from myeloablative chemotherapy (eg, infertility), and the need for long-term safety data.

TREATMENT OF COMPLICATIONS

- Educate patients to recognize signs and symptoms of complications and conditions that require urgent evaluation. Balanced fluid status and oxygen saturation of at least 92% are important to avoid exacerbation during acute illness.

- RBC transfusions are indicated for (1) acute exacerbation of baseline anemia (eg, aplastic crisis, hepatic or splenic sequestration, or severe hemolysis); (2) acute chest syndrome, stroke, intrahepatic cholestasis, or acute multisystem organ failure; and (3) preparation for procedures requiring general anesthesia.

- Hydration and analgesics are mainstays of treatment for vasoocclusive (painful) crisis. Administer fluids IV or orally at 1–1.5 times the maintenance requirement; monitor closely to avoid volume overload. Consider an infectious etiology and initiate empiric therapy if indicated.

- Use **nonsteroidal anti-inflammatory drugs (NSAIDs)** or **acetaminophen** for mild to moderate pain. Consider adding an opioid if mild to moderate pain persists (eg, **codeine** or **hydrocodone**).

- Treat severe pain aggressively with an opioid, such as **morphine**, **hydromorphone**, **fentanyl,** or **methadone**. Avoid **meperidine** due to accumulation of the normeperidine metabolite, which can cause neurotoxicity. Consider **ketamine** for opioid-dependent or opioid-tolerant patients with acute or chronic sickle cell pain. Titrate IV opioids to pain relief and then administer as a scheduled dose or continuous infusion with as-needed dosing for breakthrough pain. Patient-controlled analgesia is commonly utilized.

- Treatment of chronic pain in SCD requires an interprofessional team approach. Guidelines for chronic pain management are available.

- Promptly evaluate fever of 38.5°C (101.3°F) or higher. Empiric antibiotic therapy should provide coverage against encapsulated organisms (eg, **ceftriaxone** for outpatients [unless if used in previous 8 weeks, give ampicillin], **clindamycin** for cephalosporin-allergic patients). Add a macrolide antibiotic if *M. pneumoniae* is suspected.

- For acute chest syndrome, initiate incentive spirometry; appropriate fluid therapy; broad-spectrum antibiotics, including a **macrolide** or **quinolone** in adults; and, for hypoxia or acute distress, oxygen therapy. Other potential therapies include steroids and nitric oxide.

- Priapism has been treated with analgesics, antianxiety agents, and vasoconstrictors to force blood out of the corpus cavernosum (eg, **phenylephrine** and **epinephrine),** and vasodilators to relax smooth muscle (eg, **terbutaline** and **hydralazine**).

- Treatment of aplastic crisis is primarily supportive. Blood transfusions may be indicated for severe or symptomatic anemia.

- Hydration and blood transfusions are indicated to treat hypovolemia associated with splenic sequestration. Manage recurrent episodes with observation and splenectomy. Consider chronic transfusions in children younger than 2 years of age to delay splenectomy until the age of 2 years. Splenectomy is an option for chronic hypersplenism.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate patients on a regular basis to establish baseline symptoms, monitor changes, and provide age-appropriate education.

- Evaluate CBC and reticulocyte counts every 3–6 months up to 2 years of age, then every 6–12 months. Screen HbF level annually until 2 years of

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age. Evaluate renal, hepatobiliary, and pulmonary function annually. Screen patients for retinopathy.

- Assess efficacy of hydroxyurea by monitoring the number, severity, and duration of sickle cell crises.

See Chapter 129, Sickle Cell Disease, authored by Jin Han, Santosh L. Saraf, and Victor R. Gordeuk, for a more detailed discussion of this topic.

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